Remarks

Claims 80, 81, 90-97 and 100-108 are pending in this application; of these, claims 91-97 have been withdrawn from consideration. No amendments are being made herewith.

Summary of Examiner's Interview

Applicants thank Examiners Pagonakis and Fetterolf for the courtesy of a telephonic interview with Applicants' representatives Drs. Tanya M. Harding and Michael D. Hammer on August 3, 2011, during which the pending rejections were discussed. While agreement was not reached on all issues, Applicants believe that this response clarifies Applicants' position regarding the issues discussed in the interview.

Rejections under 35 U.S.C. §102(b)

Claims 80, 81, 90 and 100-108 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Japanese Patent No. 10212235 (hereafter JP10212235) as evidenced by the National Cancer Institute Slide entitled "What is tumor angiogenesis?" (hereinafter the NCI Slide), and as evidenced by Patel *et al.* (*Biochim et Biophys Acta*, 1766:23-41, 2006). Applicants traverse this rejection for the following reasons.

JP10212235 does not describe detecting and monitoring inhibition of angiogenesis or reduction in tumor growth in a subject, required by Applicants' claims 107 & 108

Applicants note that the methods of claims 107 and 108 recite steps for "detecting or monitoring" inhibition of angiogenesis (claim 107) or reduction in tumor growth (claim 108). No assays of tumor growth or angiogenesis in a subject are described by JP10212235. Thus, JP10212235 does not describe "detecting or monitoring angiogenesis" or "detecting or monitoring tumor growth" in a subject. The MPEP at §2131 states that "to anticipate a claim, [a] reference must teach every element of the claim." Because JP10212235 does not describe the "measuring or detecting" steps of claims 107 and 108, it cannot and does not anticipate these claims. Applicants request withdrawal of this rejection of at least claims 107 and 108, and allowance of these claims.

Anti-tumor activity is not necessarily an anti-GRP activity

Applicants understand that the Office has taken the position that Applicants' claimed invention is inherently disclosed by JP10212235. The MPEP at §2112 describes the "Requirements for Rejections Based on Inherency." In describing the rationale or evidence necessary to establish inherency, the MPEP states that "the fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (citations omitted; emphases added).

The pending claims are directed to methods of inhibiting an aberrant GRP activity. JP10212235 does not teach (explicitly or implicitly) that Compound I inhibits an aberrant GRP activity. Applicants again submit that JP10212235 alone or in combination with Patel *et al.* or the NCI slide does not "make clear that the missing descriptive matter [the ability of Compound I to inhibit aberrant GRP activity] is necessarily present" in JP10212235. In support of Applicants' position that JP10212235 does not inherently anticipate the pending claims, submitted herewith is a Declaration by Dr. James L. Mulshine, who is skilled in the art of cancer biology.

The Office acknowledges that "JP10212235 is silent as to the effect of the elected compound to inhibit an activity of a gastrin releasing peptide" (Office action, at page 4). But the Office asserts that "the administration of the claimed compound to patients suffering from cellular proliferative disorders is expected to necessarily have the claimed effect" (*Id.*). This presupposes, incorrectly, that all cancer patients are suffering from an aberrant activity of gastrin

releasing peptide. Dr. Mulshine explains that, contrary to this assertion, the complexity of tumor generation makes it impossible to make this generalization in the absence of supporting evidence – which is not found in any of the cited references:

> The transformation of a normal cell into a cancerous cell involves the possible perturbation of myriad cellular pathways. The development of a cancerous cell into a tumor and the progression of that tumor into a life-threatening disease are equally complex. Thus, in describing generic Compound I as an "anti-tumor compound" JP10212235 is potentially describing hundreds of possible biological activities. Moreover, even within the same tumor type, there are frequently subpopulations of cells that possess disparate biological characteristics. Notwithstanding the listing in Patel *et al.* of tumor types that express GRP and/or the GRP receptor, there will exist populations of cells in these tumors that do not express these proteins. Thus, GRP and/or the GRP receptor will not necessarily be expressed in the tumors listed in JP10212235.
>
> The principle that a characteristic may be present in one cell population of a tumor type, but absent in another cell population of the same tumor type is illustrated by Moody *et al.* (*J. Cell. Biochem. Supp.*, 24:247-256, 1996; submitted with the Request for Continued Examination of April 28, 2011 as Exhibit AA). Moody *et al.* assay for the presence of the GRP receptor in several small cell lung cancer cell lines and several non-small cell lung cancer cell lines. Moody *et al.* observed that the GRP receptor is abundantly present in many, but not all of the cell lines tested. Table I of Moody *et al.* shows that only 42% of small cell lung cancer and 32% of non-small cell cancer cell lines tested express the GRP receptor at levels of any biological significance. Thus, an aberrant GRP activity would affect less than half of the cell lines tested, and a treatment targeting that activity would only be effective 42% and 32% of the time, respectively.
>
> Because of the multiple levels of complexity associated with tumor development, it would be incorrect to assume that all cancer patients are suffering from an aberrant activity of gastrin releasing peptide, and one of skill would not assume anything about the properties of a tumor or tumor treatment in the absence of experimental evidence that characterizes the tumor or treatment. JP10212235 provides no data that would allow one of skill to identify the biological activity that is targeted by Compound I, and does not imply that an aberrant GRP activity is being targeted. JP10212235 supports its assertion that Compound I is effective by two experimental assays, but neither of the assays identified a molecular target for Compound I. In the first assay, a subset of nine species of Compound I (Compounds 14, 44, 45, 63, 64, 70, 71, 78, and 125) were tested for the ability to inhibit proliferation of 54 cancer cell lines. Although many of the tested compounds inhibited proliferation, JP10212235 does not present data for all of the compounds (*see* for example Table 30). In the second assay of the "anti-tumor" effect, Compound 44 was administered to a mouse that was injected with a leukemia cell line. The length of time that the mouse survived in the presence or absence of the Compound was then compared. No assay as to the *in vivo* effect of Compound 44 on the leukemia was performed.

In contrast to the relatively uncharacterized effect described in JP10212235, the pending claims are directed to specific inhibition of an aberrant activity of GRP by a small molecule mimetic of a GRP neutralizing antibody (Compound 77427, referred to as Compound XV' in the claims). Compound 77427 is able to compete with MoAb 2A11 for specific binding to GRP (*see* specification, at page 17, lines 10-16, and Table 1, pages 18-19). As with any specific molecular interaction, the ability for Compound 77427 to bind to GRP results from its shape and charge. Just as changes to an antibody structure will change its binding specificity, so too changes to a small molecule compound (such as Compound 77427) will also change its binding specificity, and by extension biological activity. Therefore, without demonstrating that Compound I and its species share the ability to bind to and inhibit GRP, I would not assume that Compound I will necessarily bind and inhibit GRP, just because GRP is a known tumor promoting factor.

JP10212235 lists Compound 105 as a species of Compound I. Compound 105 is the same as claimed Compound 77427, but apart from being listed as a species of Compound I, Compound 105 is not further described in JP10212235. It is not among the nine compounds tested for anti-proliferation activity, and it is not the used in the *in vivo* survival assay of a mouse injected with leukemia. Previously, the Office was provided with a composite list of the Compounds that were used in the experiments of JP10212235, in comparison to Compound 105 (submitted with the Request for Continued Examination on April 28, 2011 as Exhibit DD). As presented in Exhibit DD, the nine compounds tested by JP10212235 have a striking similarity: a large cyclic functional group at position R3. This large functional group is entirely absent from Compound 105. Because of this substantial difference in structure, and notwithstanding any activity shared by Compounds 14, 44, 45, 63, 64, 70, 71, 78, and 125, I would not expect Compound 105 to share the same specific activity with these compounds. Likewise, I would not expect the tested compounds to share the same specific activity as Compound 105. Moreover, because of the substantial differences in chemical structure between all of the 131 species of Compound I, I would not expect there to be any necessarily shared characteristic of all of the species of Compound I without supporting data of such a shared characteristic. (Mulshine Declaration, ¶¶5.2-5.6)

Thus, JP10212235 alone or in combination with Patel *et al.* does not "make clear that the missing descriptive matter [the ability of Compound I to inhibit aberrant GRP activity] is necessarily present" in JP10212235 to describe to one of skill in the art that the indicated anti-tumor activity is necessarily an anti-GRP activity.

Interaction with GRP is not a necessary characteristic of Compound I

Dr. Mulshine indicates in his Declaration (as quoted above) that without supporting data, he would not expect the species of Compound I to necessarily share the biological characteristics of Compound 77427, due to structural differences between the listed species. To support this argument, submitted herewith is a Declaration by Dr. Frank Cuttitta and supporting Exhibits EE

and FF. In his Declaration, Dr. Cuttitta describes the assay of a species of Compound I, Compound 109, for the ability to block the binding of a GRP neutralizing monoclonal antibody. Dr. Cuttitta describes the reasoning behind this assay as follows:

> In the Declaration submitted with the Request for Continued Examination on April 28, 2011 (hereinafter "the April 2011 Declaration"), I explained why one of skill in the art would not necessarily equate every compound described as an "anti-tumor compound" with a compound that can inhibit an activity of GRP (*see* ¶¶5.1-5.3, 7.1, 7.3 and 7.4). I further note that none of the compounds tested for anti-tumor activity in JP10212235 is a known GRP inhibitor. Moreover, Compound 77427 (labeled Compound 105 in JP10212235) is not used in any experiment in JP10212235, and has a substantially different chemical structure from any of the compounds that were used in the experiments presented in JP10212235 (*see* Exhibit DD, submitted with the Request for Continued Examination on April 28, 2011).
>
> Previously, I described the identification of Compound 77427 as a small molecule mimetic of the GRP functional antagonist, monoclonal antibody 2A11 (*see* ¶8 of the September 2010 Declaration). I also previously noted that "just as changes in an antibody's peptide structure may significantly affect its binding specificity, so too changes in chemical structure of a small molecule mimetic will affect its activity" (*see* ¶7.6 of the April 2011 Declaration). Thus, notwithstanding the assertions of JP10212235 or the Office, one of skill would not infer any property of Compound 105 from any of the other species of Compound I. Quite the contrary, in the absence of data to demonstrate a specific shared biological property, one of skill in the art would assume that compounds of different structure will possess different biological activities.
>
> To test this assumption for Compound 77427, two additional compounds were recently assayed in my lab for specific binding to GRP (as determined by the ability to block the interaction between monoclonal antibody 2A11 and GRP). The first compound tested, NSC 619198 is similar to NSC 77427 (Compound 77427), and is identical to Compound 109 of JP10212235. The second compound tested, NSC 636346, is not described in JP10212235, but was randomly selected from the National Cancer Institute Developmental Therapeutics Program (DTP) pool of small molecules containing ring structures. Additionally, Compound 77427 and bovine serum albumin (BSA) were used as positive and negative controls, respectively.
>
> As noted above, the affinity of each compound for GRP was tested by assessing the ability of the compound of interest to disrupt the binding of the GRP neutralizing antibody 2A11 to solid-phased GRP. The results of this assay are attached as Exhibit EE. (Cuttitta Declaration, ¶¶5-8)

Dr. Cuttitta further describes the results of the assay as follows:

> Exhibit EE presents three charts, each of which shows the average of twelve assays of each indicated compound (last three numbers are shown), using solid phased GRP at 100 ng/50 µl, 50 ng /50 µl or 25 ng/50 µl. Each chart also indicates whether the test

> compound was added separate from or jointly with the antibody. At all three GRP concentrations, NSC 77427 significantly inhibits antibody binding ($p<0.001$), as shown by the reduction in light absorbance in comparison to the BSA negative control. In contrast, neither of the other test compounds significantly inhibited antibody binding in comparison to BSA.
>
> The results presented in Exhibit EE demonstrate that the moderate difference in structure between NSC 77427 and NSC 619198 produces a **significant** change (reduction) in the ability of NSC 619198 to bind to GRP. I would not expect other species of Compound I with greater differences in structure from Compound 77427 to "regain" any ability to bind to GRP. This observation also demonstrates that notwithstanding any of the assertions or data presented in JP10212235, the ability to bind to GRP and affect a GRP activity is not a universal, necessary characteristic of all species of Compound I. (Cuttitta Declaration, ¶¶13-14)

Dr. Mulshine also reviewed Dr. Cuttitta's assay and concurred with this interpretation of the data:

> I understand that Dr. Cuttitta has tested a species of Compound I, Compound 109 (NSC 619198) and which is structurally similar to Compound 77427, for the ability to block the binding of MoAb2A11 to GRP. I have reviewed this data, which is provided herewith as Exhibit EE. I have also reviewed Dr. Cuttitta's Declaration, in which he describes the experiments and data shown in Exhibit EE. I concur with Dr. Cuttitta's interpretation that the data shown in Exhibit EE demonstrates that Compound 109 does not significantly block the ability for MoAb2A11 to bind to GRP. This data not only confirms the assumption that experimental evidence is necessary to prove that a class of compounds share the same specific activity, but it also supports the conclusion that the "anti-tumor activity" of described by JP10212235 is not an anti-GRP activity necessarily shared by Compound I and all of its species. (Mulshine Declaration, ¶5.7)

As Drs. Cuttitta and Mulshine note, the inability of Compound 109 to bind to GRP demonstrates that the ability to affect an aberrant GRP activity is not a necessary characteristic of Compound I, and it is unlikely that other species of Compound I, apart from Compound 77427, possess this characteristic. Thus, as Dr. Mulshine further notes, any purported anti-tumor activity of Compound I is not an anti-GRP activity. Compound 77427 is listed, but never tested experimentally in JP10212235. Thus, JP10212235 cannot and does not explicitly or inherently describe inhibition of an aberrant GRP activity.

The patient populations in JP10212235 and Patel *et al.* are not the same

Claims 90 and 100 both include steps for "selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity." The Office asserts that the listings of tumor types in

Patel *et al.* and JP10212235 are sufficient to satisfy the selecting step of claims 90 and 100 because the Office asserts that the tumors (and thus patient populations) are the same. Applicants disagree. In his Declaration, Dr. Mulshine notes the non-overlapping lists of tumors between the two references, and describes the implications of this disparity:

> The Office asserts that Patel *et al.* evidences that, by describing an anti-tumor activity, JP10212235 is inherently describing an ant-GRP activity. This is not so. Patel *et al.* describes GRP as an agent implicated in many cancers, and describes the cell types known to express GRP and the GRP receptor. But Patel *et al.* does not describe all of the tumor types listed by JP10212235. In particular Patel *et al.* does not describe leukemia as expressing GRP and/or the GRP receptor. Indeed, it is known that GRP is not implicated in development and progression of leukemia. In contrast, JP10212235 describes leukemia as a tumor type that may be treated using Compound I and its species. By indicating that Compound I and its species are effective against a group of cancers that includes leukemia, JP10212235 implies that a biological activity other than an aberrant GRP activity is targeted by Compound I. Thus, contrary to the Office's assertion, Patel *et al.* proves that JP10212235 is not teaching inhibition of a GRP activity. Similarly, because the group of tumors described by JP10212235 includes leukemia, the described tumor types, and consequently described patient population, is not the same as that described by Patel *et al.* This is because a group of patients that includes patients with a non-GRP-associated tumor have not been "selected" for having an aberrant GRP activity. Thus, Patel *et al.* also proves that JP10212235 does not inherently contain a step of selecting for a patient who is aberrantly expressing GRP. (Mulshine Declaration, ¶6.2)

Thus, because JP10212235 administers its compounds to treat tumors of a group that includes leukemia, the patient population is not necessarily one that is "expressing GRP aberrantly or has an aberrant GRP activity." Therefore, the selection step of claims 90 and 100 is not inherent to JP10212235 and JP10212235 cannot and does not anticipate these claims.

Anti-tumor activity* is not necessarily *anti-angiogenesis activity

Claim 100 is directed "to inhibiting angiogenesis-mediated growth of a solid tumor." The Office asserts that "treatment of a tumor would necessarily inhibit angiogenesis since angiogenesis is responsible for progression of the disease." Applicants disagree. Previously, Applicants discussed that angiogenesis, while a factor in tumor progression is not necessarily the target of any given "anti-tumor" therapy. Dr. Mulshine further explains this principle as follows:

> As discussed above, development and progression of a tumor is the combination of myriad biological processes. Angiogenesis is only one category of processes necessary for tumor development and progression. In addition to angiogenesis, a cancer cell must be able to proliferate. The NCI slide provides no evidence to the contrary. The NCI slide

> merely illustrates that tumors are able to induce angiogenesis to facilitate tumor growth. The NCI slide makes no statement that all anti-tumor treatments must necessarily inhibit angiogenesis. A cancer cell may secrete factors to stimulate robust angiogenesis, but if the cancer cell is unable to proliferate uncontrollably it will not develop into a tumor and will not progress into a life-threatening disease. Thus, a given anti-tumor therapy might target angiogenesis, but it might alternatively target cellular proliferation. While treatments exist that target both proliferation and angiogenesis, many treatments target these processes individually. This variety of anti-tumor targets is well known and is illustrated by the list of treatments with varying targets in the table on page 118 of Butowski and Chang, *Cancer Control*, 12:116-124, 2005, which was submitted with the Request for Continued Examination on April 28, 2011 as Exhibit CC. I note that while Butowski and Chang discuss the importance of angiogenesis in glioma development, not all of the potential therapies discussed therein target angiogenesis.
>
> Because different anti-tumor treatments can target different processes, I would not assume any particular target for a given "anti-tumor treatment." JP10212235 does not state that Compound I and its species can be used to inhibit angiogenesis. Not does JP10212235 describe any experiments that use Compound I as an anti-angiogenic agent. Indeed, the only anti-tumor activity indicated by JP10212235 is an anti-proliferative activity. (Mulshine Declaration, ¶¶ 7.1-7.2)

Thus, treatment of a tumor does not "necessarily inhibit angiogenesis." Because JP10212235 does not explicitly of implicitly describe inhibition of angiogenesis, it cannot and does not anticipate claims 100-103, 107 and 108.

For the foregoing reasons, Applicants submit that the pending claims are not anticipated by JP10212235. Applicants request that the novelty rejection of claims 80, 90 and 100-108 be withdrawn.

Rejoinder of Withdrawn Claims

Applicants submit that based on the foregoing arguments, generic claims 80 and 90 are in condition for allowance. Applicants request that claims 91-97 be rejoined, examined, and allowed at this time.

Conclusion

Based on the foregoing amendments and arguments, the pending claims are in condition for allowance, and notification to that effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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